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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,836	06/01/2001	Shikha P. Barman	08191-018001	3677

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,836	BARMAN ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-16,21-24,26-29,31-34 and 37* is/are pending in the application.

4a) Of the above claim(s) _-_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-16,21-24, 26-29,31-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

9,00,

DETAILED ACTION

Applicant's response of 07/25/2005 has been entered. No amendments were made by the present reply. Claims 1-16, 21-29, 31-34, and 37 are presently pending in the application.

Claim Rejections – 35 USC § 102(e)

Claims 1-4, 6-7, 9-16, 29, and 37 are rejected under 35 USC 102(e) as being anticipated by Papahasdjopoulos *et al.* (US Pat No. 6,803,053).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the microparticles of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the

fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Response to Arguments – 35 USC § 102(e)

Claims 1-4, 6-7, 9-16, 29 and 37 were rejected under 35 USC § 102(e) in the first office action dated January 25, 2005.

Applicant's Arguments of July 25, 2005 have been fully considered but not found to be persuasive.

Applicant argues that the claimed microparticles differ from the complexes disclosed in Papahadjopoulos et al, U.S. Patent No. 6,803,053 ("Papahadjopoulos") because the claimed microparticles contain a polymeric "matrix" (e.g., a material in which something is enclosed or embedded), whereas there is no indication in Papahadjopoulos that the hydrophilic polymer used therein forms a "matrix".

Such is not persuasive. As was stated in the first office action, Papahadjopoulos specifically teach a lipid:nucleic acid complex containing other compounds such as a polycation and hydrophilic polymers (e.g. PEG-DSPE). The Applicant's own specification defines polymeric matrix as one or more synthetic polymers having solubility in water of less than about 1mg/l. As such, the compositions of Papahadjopoulos anticipate the composition of claim 1 in the instant application. Further, in column 10, second full paragraph, Papahadjopoulos states: "It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic pad at the exterior surface, thereby stabilizing the entire complex". The applicant is therefore arguing the absence of the term "matrix" in the quote by Papahadjopoulos. Applicant's attention is drawn to Papahadjopoulos, column 35, Example 14, wherein reference is made to "Mal-PEG-DSPE linkers pre-incorporated into the liposome lipid matrix".

Applicant's second argument alleges that Papahadjopoulos does not disclose a composition containing both the polymeric matrix and the lipid components of the claimed microparticles. Applicant argues that the "polymeric matrix" and the "lipid" are two distinct components that must

both be present in the claimed microparticles and that claim 37 further limits claim 1 by requiring that the "lipid" be PEG-DSPE).

Such is not persuasive. In column 3, last two paragraphs and first paragraph of column 4, Papahadjopoulos teaches lipid:nucleic acid complexes prepared by combining a nucleic acid with an amphiphilic cationic lipid and then combining the complex thus formed with a hydrophilic polymer, selected from the group consisting of PEG-DSPE and others. As such, the composition of Papahadjopoulos anticipates the composition of claim 1. The fact that PEG-DSPE is both a hydrophilic polymer and a lipid is irrelevant.

Applicant's third argument is directed to a limitation of claim 1 that requires the claimed microparticle be less than about 100 microns in diameter. Applicant argues that Papahadjopoulos provides no description of a non-liposome composition that would necessarily be less than about 100 microns in diameter.

Such is not persuasive because Applicant's argument does not apply to the grounds upon which the rejection relies. The microparticle of claim 1 comprises a polymeric matrix, a lipid and a nucleic acid. Claim 1 is drawn to a microparticle that is less than about 100 microns in diameter, not the polymeric matrix alone. In section 10, lines 55-58, Papahadjopoulos, referring to lipid nucleic acid complexes, states: "the lipids need not be provided as a liposome. It is also recognized that after complexation, the lipid:nucleic acid complex may no longer exist as a true vesicle and therefore is not generally regarded as a liposome".

In column 36, Example 15, Papahadjopoulos describes the preparation of lipid-DNA complex microparticles wherein a suspension of lipid-DNA microparticles measuring between 0.26 and 0.56 microns were used for subsequent preparation of microparticles with conjugated and non-conjugated PEG-DSPE. Since Papahadjopoulos teaches the composition of claim 1 in the instant application, then a microparticle resulting from such composition would inherently have the properties of the microparticle of claim 1, including a diameter of less than about 100 microns. The inherent property of the size limitation is therefore present in the disclosure of the prior art. Further, "where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established". In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Hence, the rejection is maintained for reasons of record and expanded upon by the commentary given above (Supra).

Claim Rejections – 35 USC § 103(a)

Claims 1-4. 6, 7-16, 29, 32-34, and 37, embracing a polymeric microparticle entrapping lipid:nucleic acid complexes, are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahasdjopoulos *et al.* taken with Rolland (US Pat NO. 6,040,295), and further in view of Lusford (US 2002/0182258 A1).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the complexes of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the

fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles with a diameter of less than about 100 microns that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex, nor does Papahasdjopoulos *et al.* teaches explicitly that an antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

In addition, Lunsford teaches a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized less than about 100 microns, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* pars 0055, Table 3, pars 0054, 0052, claims 36 and 37.

As such, it would have been obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahasdjopoulos *et al.* One of ordinary skill in the art

would have been motivated to employ the polymeric microparticles having a size of less than 100 microns in diameter of Lunsford, for example, in the complexes of Papahasdjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations. One also would have been motivated to do so in order to enhance the controlled release of the lipidic:nucleic acid complexes of Papahasdjopoulos *et al.* and protect the plasmid vectors from degradation during its circulation *in vivo.*

While Rolland does not teach that the microparticle has a diameter size of 50 microns, it would have been obvious for one of ordinary skill in the art to have made, as a matter of design choice, microparticles with a diameter such so long as the microparticles could still entrap the lipidic:nucleic acid complexes of Papahasdjopoulos *et al.* Note that the microparticles of different sizes of less than 100 microns are routinely made in the prior art by filtering and/or emulsion/mixing techniques, given the disclosure of Lunsford, and particularly since the size limitation does not appear to contribute any inventive feature to the invention.

It would also have been obvious for one of ordinary skill in art to employ a DNA coding for an immunogen or multiple immunogenic peptides in the DNA complexes of Papahasdjopoulos for delivery and expression at a desired target tissue such as a a mucosal tissue because Lunsford is one of many exemplified references that teach that a polymeric microparticle entrapping plasmid DNA coding for a protein of interest such as an antigenic polypeptide can be used to deliver and express such at a mucosal tissue such as vagina tissue.

One of ordinary skill in the art would have expected that such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity, and that the incorporation of additional polymeric microparticles would enhance the controlled release and bioavailability of the nucleic acid/lipidic complexes. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* as the result of a controlled release from the polymeric microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-4. 6, 7, 9-16, 26, 29, 32-34, and 37, embracing a polymeric microparticle encapsulating the lipid:nucleic acid complex, are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahasdjopoulos *et al.* taken with Rolland (US Pat NO. 6,040,295), and further in view of Mathiowitz (US Pat No. 6,677,313).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the complexes of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex, nor does Papahasdjopoulos *et al.* teaches explicitly that an antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

In addition, Mathiowitz teach a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized between one and ten microns, a stabilizer such as anhydride monomers, oligomers, organic dyes or metal compounds, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* see column 2, lines 17-56, column 4, last par., columns 7 and 8, and columns 12 and 13. Plasmid vectors including a targeting ligand is disclosed on column 19, lines 21-23.

As such, it would have been obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Mathiowitz, to entrap the lipid:nucleic acid:PEG-DSPE complexes of Papahasdjopoulos *et al.* One of ordinary skill in the art would have been motivated to employ the polymeric microparticles of Mathiowitz, or Jones, for example, in the complexes of

Papahasdjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations.

It would also have been obvious for one of ordinary skill in art to employ a DNA coding for an immunogen or multiple immunogenic peptides in the DNA complexes of Papahasdjopoulos for delivery and expression at a desired target tissue such as a a mucosal tissue because Mathiowitz is one of many exemplified references that teach that a polymeric microparticle entrapping plasmid DNA coding for a protein of interest such as an antigenic polypeptide can be used to deliver and express such at a mucosal tissue such as vagina tissue.

One of ordinary skill in the art would have expected that such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity, and that the incorporation of additional polymeric microparticles would enhance the controlled release and bioavailability of the nucleic acid/lipidic complexes. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* as the result of a controlled release from the polymeric microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 21-24, 27, and 31 are rejected under 35 USC 103(a) as being unpatentable over Papahasdjopoulos *et al.* taken with Carson (US 2003/0109469), as evidenced by Adema (US Pat No. 6,500,919).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the microparticles of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the DNA could code for a MHC-1 binding antigen or multiple MHC-1 binding antigens.

However, at the time the invention was made, the concept of employing a peptide or arrays of peptides known in the prior art in a plasmid expression vector for use as an immunogenic composition is taught in Carson. For example, par. 59-60 on page 10-11 discloses that the plasmid vector can be constructed to encode an array of antigenic peptides of choice such as MHC peptides, cytokines, and/or T cell epitopes for tumor treatment, for example. As evidenced by Adema, MHC I binding peptides for use in vaccines such as treatment of a melanoma tumor are well known in the prior art.

Thus, it would have been obvious for one of ordinary skill in the art to employ an antigenic peptide of choice such as any known MHC I binding peptide or a combination thereof in the plasmid vector taught by the primary reference. One of ordinary skill in the art would have been motivated to

employ one more DNA fragments coding for peptides in the plasmid expression vector because Carson teaches on page 11 that the use of plasmid vector expressing an array of peptides of choice can be routinely made and is efficient to be used as a cocktail vaccine against more than antigens of choice, and because Adema teaches that MHC I binding peptides are effective for use in vaccine against tumor bearing patients such as melanoma patients.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 21-24, 27, 28, and 31 are rejected under 35 USC 103(a) as being unpatentable over Papahasdjopoulos *et al.* (US Pat No. 6,803,053), taken with Rolland and Lunsford, and further in view of Carson, as evidenced by Adema.

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a MHC-1 binding antigen, and a cationic lipid/co-lipid complex. Other than the limitation reciting a MHC-1 binding antigen encoding DNA for use in an expression vector, Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

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Papahasdjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles with a diameter of less than about 100 microns that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex, nor does Papahasdjopoulos *et al.* teaches explicitly that a MHC-1 binding antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

In addition, Lunsford teaches a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized less than about 100 microns, and a plasmid DNA coding for a protein of interest such as an antigenic MHC binding antigen, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* pars 0055, Table 3, pars 0054, 0052, claims 36 and 37.

As such, it would have been obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahasdjopoulos *et al.* One of ordinary skill in the art would have been motivated to employ the polymeric microparticles having a size of less than 100 microns in diameter of Lunsford, for example, in the complexes of Papahasdjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations. One also would have been motivated to do so in order to enhance the controlled release of the lipidic:nucleic acid complexes of Papahasdjopoulos *et al.* and protect the plasmid vectors from degradation during its circulation *in vivo*.

While Rolland does not teach that the microparticle has a diameter size of 50 microns, it would have been obvious for one of ordinary skill in the art to have made, as a matter of design choice, microparticles with a diameter such so long as the microparticles could still entrap the lipidic:nucleic acid complexes of Papahasdjopoulos *et al.* Note that the microparticles of different sizes of less than 100 microns are routinely made in the prior art by filtering and/or emulsion/mixing techniques, given the disclosure of Lunsford, and particularly since the size limitation does not appear to contribute any inventive feature to the invention.

It would also have been obvious for one of ordinary skill in art to employ a DNA coding for an immunogen or multiple immunogenic peptides in the DNA complexes of Papahasdjopoulos for delivery and expression at a desired target tissue such as a a mucosal tissue because Lunsford is one of many exemplified references that teach that a polymeric microparticle entrapping plasmid DNA coding for a protein of interest such as an antigenic polypeptide can be used to deliver and express such at a mucosal tissue such as vagina tissue.

One of ordinary skill in the art would have expected that such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity, and that the incorporation of additional polymeric microparticles would enhance the controlled release and bioavailability of the nucleic acid/lipidic complexes. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to

stabilize the plasmid vector when circulated *in vivo* as the result of a controlled release from the polymeric microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

With respect to the limitation of employing a MHC-1 binding peptide expressing vector in the method of Papahasdjopoulos *et al.* taken with Rolland and Lunsford., the concept of employing a peptide or arrays of peptides known in the prior art in a plasmid expression vector for use as an immunogenic composition is taught in Carson. For example, par. 59-60 on page 10-11 discloses that the plasmid vector can be constructed to encode an array of antigenic peptides of choice such as MHC peptides, cytokines, and/or T cell epitopes for tumor treatment, for example. As evidenced by Adema, MHC I binding peptides for use in vaccines such as treatment of a melanoma tumor are well-known in the prior art.

Thus, it would have been obvious for one of ordinary skill in the art to employ an antigenic peptide of choice such as any known MHC I binding peptide or a combination thereof in the plasmid vector taught by Papahasdjopoulos *et al.* taken with Rolland and Lunsford. One of ordinary skill in the art would have been motivated to employ one more DNA fragments coding for peptides in the plasmid expression vector because Carson teaches on page 11 that the use of plasmid vector expressing an array of peptides of choice can be routinely made and is efficient to be used as a cocktail vaccine against more than antigens of choice, and because Adema teaches that MHC I binding peptides are effective for use in vaccine against tumor bearing patients such as melanoma patients.

Thus, the claimed invention was *prima facie* obvious.

Response to Arguments – 35 USC § 103(a)

Claims 1-4, 6-16, 21-24, 27-29, 31-34 and 37 were rejected under 35 USC § 103(a) in the first office action dated January 25, 2005.

Applicant's Arguments of July 25, 2005 have been fully considered but not found to be persuasive.

Applicant argues that the entrapment of a targeting moiety-containing complex disclosed by Papahadjopoulos within a composition of Rolland (Rolland et al., U.S. Patent No. 6,040,295), Lunsford (Lunsford et al., U.S. Published Application No. 2002/0182258, or Mathiowitz (Mathiowitz

et al., U.S. Patent No. 6,677,313) would have been expected to partially or completely mask the targeting moieties and thereby reduce or eliminate their targeting function.

Such is not found to be persuasive. In response, Papahadjopoulos describes a microparticle characterized by targeting moieties attached thereto, for the delivery of lipid/nucleic acid complexes to a desired target. In column 2, lines 44-56, Rolland also describes the use of targeting ligands for the enhanced translocation of nucleic acids to specific tissues or cells. Lunsford claims (section 21, claim 1), a microparticle comprising a polymeric matrix, a lipid and a nucleic acid molecule that is not encapsulated. Neither Papahadjopoulos, Rolland or Lunsford require the encapsulation method described by Mathiowitz. The reference to Mathiowitz was used for an entirely different purpose and to address a separate limitation. Mathiowitz was not used to require the products of Papahadjopoulos, Rolland or Lunsford be encapsulated. Finally, in column 10, lines 44-45, Papahdjopoulos specifically states, "if the particle is a vesicle, the linker/protein molecules will only be present on the outer surface". Therefore Applicant's assertion that the targeting moieties would have been expected to be partially or completely masked is not supported.

Regarding the rejection of claims 21-24, 27, and 31, Applicant argues that neither Carson (Carson et al., U.S. Published Application No. 2003/0109469), nor Adema (Adema et al., U.S. Patent No. 6,500,919) add the "matrix" component or the non-liposome composition that is allegedly lacking in Papahadjopoulos. Applicant refers to the response provided for the 102(e) rejection. The Examiner respectfully disagrees on the same grounds outlined in the commentary given above (Supra). In addition, Applicant's attention is drawn to page 18 of the office action dated January 25, 2005, wherein the polymeric microparticles of Lunsford are addressed relative to the claims of the instant application. Lunsford specifically teaches (abstract of the patent) microparticles made up of a polymeric matrix, a nucleic acid and a lipid, wherein at least 90% of the microparticles have a diameter less than about 100 microns. Further, regarding the composition of Papahadjopoulos, "the inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). Therefore, neither Carson nor Adema need to add to Papahadjopoulos what is not lacking.

Similarly, Applicant's final argument to the rejection of claims 21-24, 27, 28, and 31 is based on the previously stated assertion that entrapment of the complex of Papahadjopoulos within a

composition of Rolland or Lunsford would mask the targeting moieties. The Examiner respectfully disagrees on the same grounds outlined in the commentary given above (Supra).

Hence, the rejection is maintained for reasons of record and expanded upon by the commentary given above (Supra).

Applicant's attention is drawn to the omission from line 1 on page 9 of the office action dated January 25, 2005. Claim 26 should have been included in the rejection under 35 USC 103(a), as the substance and limitations of the claim (i.e. immunogenic peptides) were properly addressed in the second paragraph, page 12 of the office action dated January 25, 2005.

CONCLUSION

The rejections are maintained in view of the response to arguments and for reasons of record.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(571) 272-0532**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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